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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/362,286	07/27/1999	ANUPAMA K. NADKARNI	CPI-099	6674

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EXAMINER
MURPHY, JOSEPH F

ART UNIT	PAPER NUMBER
1646	

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19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/362,286	Applicant(s) NADKARNI ET AL.	
	Examiner Joseph F. Murphy	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 43-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 43-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The request filed on 5/30/2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09362286 is acceptable and a CPA has been established. An action on the CPA follows.

Formal Matters

Claims 44-59 were added in paper No. 18, 5/30/2002. Claims 1-14, 43-59 are pending and under consideration.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14, 43-59 are rejected under 35 U.S.C 112, first paragraph, because the specification, while being enabling for a mutant IL8 receptor and a mutant galanin receptor, does not reasonably provide enablement for any other mutant mammalian G protein coupled receptor. There is not adequate guidance as to the nature of the mutant mammalian G protein coupled receptor which Applicants claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with this claim.

Applicant argues that the specification sets forth methods for making mutant G protein coupled receptors, and methods for screening for mutant GPCR's which have increased

signaling. However, the unpredictability of the protein art is shown in Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Mikayama et al. (1993) which teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape

characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein.

There is no guidance provided in the specification as to how one of ordinary skill in the art would generate a CXCR3 polypeptide other than those exemplified in the specification. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors considered to be relevant in the instant case are set forth below:

(1) the breadth of the claims - The claims included in the instant rejection recite the functional limitation that the encoded protein can generate a signal greater than the signal generated by a wild-type protein.

(2) the nature of the invention - The instant invention is a mutant protein.

(3) the state of the prior art - The Mikayama and Voet references demonstrate that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function.

(5) the level of predictability in the art - The Mikayama and Voet references demonstrate the unpredictability of the protein art.

(6) the amount of direction provided by the inventor - Applicant has only taught a mutant IL-8A and mutant galanin receptor.

(7) the existence of working examples - Working examples are provided only for a mutant IL-8A and mutant galanin receptor, not any other mutant receptor protein.

(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Given the breadth of claims 1-14, 43-59 and based upon the evidence presented in the Bowie et al. reference showing that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex, and the Mikayama et al. and Voet et al. references which demonstrates that the change of a single amino acid can radically alter protein function, and absent sufficient evidence to the contrary, a preponderance of the evidence demonstrates that it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claims 1-14, 43-59 are rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant argues that the claims set forth three structural features of the claimed receptor, and that therefore the claims meet the written description requirement. However, as set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common

attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only two species within the genus.

Claim Rejections - 35 USC § 112 second paragraph

Claims 1, 8 and 13 stand rejected, and claim 43 is rejected, under 35 USC § 112, second paragraph, for reasons of record set forth in Paper No. 10, 6/5/2000.

Applicant argues that the terms IL-8 and galanin receptors are defined in the specification. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The term "proximal" in claim 1 is a relative term which renders the claim indefinite. The term "proximal" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Claims 2-14 and 43 are rejected insofar as they depend on the recitation of the term "proximal".

Claim Rejections - 35 USC § 102

Claims 1, 5, 8, 10-11 stand rejected, and claim 43 is rejected under 35 U.S.C. 102(b) as being anticipated by Navarro et al. (WO 92/18641) for reasons of record set forth in Paper No. 10, 6/5/2000.

Navarro et al. discloses a mammalian IL8 receptor (page 10, lines 5-14). This receptor comprises a LFGA motif near the carboxy terminal (Figure 1, drawing Sheet 2, third line; Sequence Comparison A), and a seventh transmembrane domain. Navarro et al. discloses that specific receptor analogs include full-length or partial receptor proteins including an amino acid sequence which differs only by conservative amino acid substitutions, for example, substitution of one amino acid for another of the same class, or by one or more non-conservative amino acid substitutions, deletions, or insertions (page10, line 32 to page 11, line7) . Thus claims 1, 8 and 11 are anticipated.

The receptor disclosed by Navarro et al. is expressed in mammalian cells (page 18, line 21-page 19, line7), thus anticipating claim 5. The receptor cloned by Navarro et al. is human, thus anticipating claim 11.

The mutants disclosed in Navarro et al. meet the structural limits imposed by the claim, and would therefore have the same function. Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Claims 1-2, 4-5 and 11-12 stand rejected under 35 U.S.C. 102(b) as being anticipated by Bergsman et al (WO 96/18651) for reasons of record set forth in Paper No. 10, 6/5/2000.

Bergsman et al. discloses a human somatostatin receptor (page 3, line 23). The receptor comprises a PPLA motif proximal to the carboxy terminal (page21, third line; Sequence Comparison B), and a seventh transmembrane domain. Bergsman et al. discloses that mutants of the receptor may be prepared by the deletion of a portion of the sequence encoding the protein, by insertion of a sequence, and/or by substitution of one or more nucleotides within the sequence. The receptor disclosed in Bergsman et al. is expressed in human host cell lines (page 16, line 5), and yeast expression vectors are also envisaged (page 8, line 11) thus claims 1-2, 4-5 and 11-12 are anticipated.

The mutants disclosed in Bergsman et al. meet the structural limits imposed by the claim, and would therefore have the same function. Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Claims 1, 5 and 11-13 stand rejected under 35 U.S.C. 102(b) as being anticipated by Hinuma et al. (EP 0711830A2) for reasons of record set forth in Paper No. 10, 6/5/2000.

Hinuma et al. discloses a human galanin receptor (page 4, line 58 to page 5, line 8). The receptor comprises an FLSE motif near the carboxy terminal (page 58, amino acids 305-309), and a seventh transmembrane domain. Hinuma et al. discloses that the galanin receptor protein can be modified by, e.g., addition, deletion, substitution with other amino acids, etc (page 15, lines 49-50). The receptor disclosed in Hinuma et al. is expressed in 293 cells (page 18, lines 49-56). Thus, claims 1, 5 and 11-13 are anticipated.

The mutants disclosed in Hinuma et al. meet the structural limits imposed by the claim, and would therefore have the same function. Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
June 6, 2002

DAVID S. ROMEO
PRIMARY EXAMINER